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Original article

# The possible protective and therapeutic effects of ginger and cinnamon on the testis and coda epididymis of streptozotocin-induced-diabetic rats: Histological and biochemical studies

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ABSTRACT

Diabetes mellitus (DM) is a metabolic condition characterized by high blood sugar levels with serious system complications. Ginger *(Zingiber officinale)* and Cinnamon *(Cinnamomum zeylanicum)* have anti-diabetic activities. The goal of this study is to evaluate the possible protective and therapeutic effects of ginger and Cinnamon against histological, Ki67 Immunohistochemistry (IHC) and biochemical studies in testis and coda epididymis of Streptozotocin (STZ) induced diabetic rats. The experimental rats were divided into six groups: **G1** was the control, **G2** induced diabetic without treatment, **G3** was treated with ginger before induction of DM (ginger protective), **G4** were given ginger after DM induction (ginger therapeutic), **G5** were given cinnamon before induction of DM (cinnamon protective) and **G6** were given cinnamon after DM induction (cinnamon therapeutic). In diabetic rats' significant increases in fasting blood sugar and body weight were observed after three weeks. Ginger and cinnamon effectively decreased serum glucose levels. Histopathological evaluations of seminiferous tubules and coda epididymis sections from diabetic rats showed severe damage to them. Furthermore, the sections of seminiferous tubules and coda epididymis rats administered ginger and cinnamon extract showed normal structure, healthy lining epithelium and sperm contents compared to diabetic rats. The results of the study show that both Ginger and Cinnamon aqueous extracts are effective as both hypoglycemic natural supplements that can protect against diabetic-induced testicular damage as well as share in the reservation of the cauda epididymal structure and sperm contents.

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## 1. Introduction

Diabetes mellitus is characterized by hyperglycemia caused by impaired insulin production, insulin receptor sensitivity, or a combination of both (Sangi, 2018) According to estimates of IDF, the number of diabetic patients is going to increase to 642 million by 2040 (Sangi et al., 2018; Ding et al., 2015).

Diabetes mellitus is a clinical metabolic disease-causing various complication, commonly; ketoacidosis, nephropathy, and neuropathy (American Diabetes Association, 2014). One of the known main early complications is its effect on male reproductive system mainly sexual dysfunction (Ding et al., 2015; A.D.A., 2014) due to alteration of homeostatic mechanisms by hyperglycemia - induced oxidative stress (Yaribeygi et al., 2019).

Glucose-lowering medication were used for people with diabetes to prevent hyperglycemia- induced complication (Hu & Jia, 2019; Lim et al., 2020). However, medicinal drugs are not often effective, and some showed many side effects (Chaudhury et al., 2017). Because most traditional medicines have no side effects, several medicinal plants and herbs are utilized to treat diabetes mellitus (Garg et al., 2019).

Ginger (*Zingiber officinale*), as herbal medicine was used all over the world to treat a variety of clinical diseases such as cancer, inflammation and also diabetes (Anh et al., 2020). Ginger contains many bioactive antioxidants including polyphenol compounds (Idris et al., 2019) and thus, it was proved to neutralize free radicals produced by hyperglycemia (Alsherbiny et al., 2019).

Cinnamon, also called sweet wood (Greek origin), widely cultivated in tropical countries (Medagama, 2015). The herb contains many beneficial constituents including Cinnamyl acetate, eugenol,

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Cinnamaldehyde and Cinnamic acid (Ibrahim & Al-Shathly, 2015) which are responsible for the therapeutic effects of cinnamon.

One of such effects is its role in decreasing blood sugar levels (Al-Shathly et al., 2020; Talaei, 2019; Al-Shawabk & Jamal, 2019).

Ginger and cinnamon were also reported to have impact on male fertility (Banihani, 2019; Soleimani et al., 2019).

Based on previous literature, in the present study, the use of both aqueous extracts of Ginger and cinnamon were evaluated for their protective and therapeutic effects against STZ-induced histological and Ki 67 immuno-expression in diabetic rat testis and coda epididymis.

## 2. Materials and methods

### 2.1. Animals

Thirty- six male Wistar rats (3 months old, average body weight 200–250 gm) were purchased from Animal House, King Fahd Medical Research Centre (KFMRC), King Abdelaziz University, Jeddah, Saudi Arabia. Throughout the experiment, the rules of laboratory animal care were observed, and the experimental treatments were carried out according to the instructions provided by the King Abdulaziz University ethics committee. The rats were kept in standard cages at a humidity of 65 % (Temperature, 22 °C, 12/12 h light/dark cycle), and given commercial chow ad libitum and had unrestricted access to water.

### 2.2. Preparation of ginger

According to (Al-Amin et al., 2006), aqueous ginger extract was made. 50 g of ginger was pulverized into small pieces and homogenized in 75 ml cold, sterile 0.9 % NaCl in presence of some crushed ice. The homogenisation was carried out in a high speed blender for 12 min. Filtration was done and the filtrate was centrifuged at 2000 rounds per for 10 min and the clear supernatant fraction was made up to 100 ml with normal saline. The ginger preparation concentration was considered 500 mg/ml based on the weight of the starting material (50 g/100 ml). The prepared extract was stored in an Eppendorf's tube in refrigerator at 4 °C.

### 2.3. Preparation of cinnamon

Aqueous Cinnamon extract was prepared according to (Alkhamas, 2018). Cinnamon bark (500 g) was thoroughly powdered and saved airtight in cool, dry, and dark environments. The bark powders of Cinnamon (50 g) were boiled separately in (250 ml) distilled water and filtered through Whatman no: 40 filter papers. The extracts were evaporated by room temperature.

### 2.4. STZ-diabetes induction

STZ was purchased from Sigma Aldrich Chemical Company, (St. Louis, MO, USA). Rats were fasting overnight intraperitoneally injected with a single dose of STZ in 0.1 ml citrate buffer (pH 4) at a dose of (45 mg/kg /b.w) (Poornima et al., 2017). Blood glucose was determined 4 days after injection of STZ using a blood glucometer (ACCU-CHEK; Roche, Mannheim, Germany), from tail blood vein withdrawn. The current study comprised rats with fasting blood glucose (FBG) levels $\geq$250 mg/dl.

### 2.5. Experimental protocol

Rats were randomly divided according to the treatment into six groups (n = 6 for each) labelled as G1, G2, G3, G4, G5 and G6. Cinnamon and fresh ginger roots were bought from the local market in Jeddah city. The aqueous extract was given orally via stomach gavage, in dose of ginger (500 mg/kg/bw/day), and Cinnamomum (50 mg/kg/bw/day). Rats of G**1** contained control rats; **G2** rats, induced diabetic, **G3** rats, treated with ginger before induction of DM (ginger protective) (Al-Amin et al., 2006); **G4** rats, were given ginger after DM induction (ginger therapeutic); **G5** rats, were given cinnamon before induction of DM (cinnamon protective) (Alkhamas, 2018; Muhammad & Sangi, 2018); **G6** rats, were given cinnamon after DM induction (cinnamon therapeutic).

### 2.6. Assessment of body weight

The initial and final body weights for each rat were recorded.

The percent change in body weight was calculated according to (Kunle et al., 2017) using the following formula:

$$\%\ \text{Body weight change} = \text{Final body weight} - \text{initial body weight/initial body weight} \times 100$$

### 2.7. Assessment of histological tissue sampling and Immunohistochemistry (IHC) study

At the end of 4 weeks animals were euthanized under deep ether anaesthesia. Abdomen and pelvic cavities were opened, to remove the testis. It was immersed in 10 % neutral buffered formalin 24 h after which it cut transversely and processed for paraffin sections 5-µm thick stained by hematoxylin and Eosin (H&E) for general structure examination using a light microscope (Olympus BX61- USA) connected to motorized controller unit (Olympus bx-ucb, USA) and photographed by a camera (Olympus DP72, USA).

For Ki 67 immunostaining, "another serial sections of 5-µm paraffin tissue were cut, dewaxed, and rehydrated in xylene and distilled water. Antigen retrieval was then carried out in a microwave oven. 3 % hydrogen peroxide was used to quench endogenous peroxidase activity in sections for 30 min. at room temperature, followed by 15 min. of blocking with 5 % bovine serum. The sections were then incubated overnight at 4 °C in a humidified room with specific primary antibodies against Ki-67 (GB11010; Wuhan Saiweier Biological Technology, China). After being washed with PB, the sections were treated with secondary antibody and stained with 3, 3′-diaminobenzidine after being rinsed with PB. Hematoxylin was used to counterstain the slices, which were then washed in tap water". Micrographs of (IHC) were examined under a microscope (Zhao et al, 2018).

### 2.8. Assessment of morphometric study

The germinal epithelial lining height and the area percentage of cytoplasmic Ki67 reactions of both the seminiferous tubules (STs) and coda epididymis were estimated using the same camera mentioned above. The procedure was performed using H&E-stained and Ki67 stained sections. Measurements were taken in 10 non overlapping fields for each of four randomly chosen rats from each group, as indicated by Elkhateeb et al. (2014).

### 2.9. Statistical analysis

Statistical Package for the Social Science was used to analyze the data (SPSS Software Version 20, Chicago, IL, USA). The mean and standard deviation of all numeric variables were calculated (SD). The one-way analysis of variance (ANOVA) test was used to make statistical comparisons, followed by a post hoc least significant difference multigroup comparison. The one-way ANOVA test and Levine's statistic test were used to determine homogeneity of variance. $P < 0.05$ was considered statistically significant in all testis.

## 3. Results

### 3.1. Effect of ginger and cinnamon on blood glucose level and body weight

The changes in (FBG) and the (b.w) in different groups were summarized in Table 1.

### 3.2. Effect of ginger and cinnamon on testicular and coda epididymis histopathology

#### 3.2.1. Hematoxylin and eosin (H&E) stained slices under a light microscope

In Figs. 1 and 2 seminiferous tubules and coda epididymis tissue of a rat from the control group (G1), They had an ordinary shape; their epithelium was structurally intact and showed the normal association of germ cells, and normal sperm content. In (G2) Marked degenerative, vacuolar changes, presences only of residual degenerated cells. Coda epididymis tubules showed irregular outlines, atrophy lining epithelium and loss cilia with decrease sperm in some tubules. On the other hand, (G3) shows normal (ST) with full thickness spermatogenic layers. Similar finding was observed in (G4) few changes in (ST). Regarding coda epididymis examined for all groups, it was observed in both protective and therapeutic groups, they showed healthy lining epithelium and sperm contents compared to diabetic rats. In (G5) and (G6) evident improvement of changes induced by diabetes were observed in both (ST) and epididymis with minor irregular outlines in the latter.

#### 3.2.2. Morphometric study of (STs) germ cell layer thickness and coda epididymis epithelial height

*3.2.2.1. Thickness of seminiferous tubules germinal epithelium.* The mean thickness of germinal epithelium of S.Ts. in diabetic rats was significantly lower than in controls, but it was significantly higher in all protective and therapeutic groups **(G3, G4, G5, G6)** compared to the group **(G2)** Fig. 3.

*3.2.2.2. Thickness of coda epididymis germinal epithelium:.* Regarding morphometric changes in coda epididymis germinal epithelium lining was significant increase in epithelial thickness in **(G2)** compared to **(G1)**. Significant decrease was observed in the **(G3) & (G5)** protective and **(G4) & (G6)** therapeutic groups compared to the group **(G2)** Fig. 4.

### 3.3. Effect of ginger and cinnamon on testicles and coda epididymis immunoexpression of Ki67

Ki 67 was stained immunohistochemically to evaluate the alteration of proliferative status of spermatogenic cells. In **(G1)** rat testis immunopositive staining for Ki67 was observed, in **(G2)** there was marked decrease in such immunopositive staining, in testis of both protective and therapeutic groups. Administration of ginger and cinnamon preserved and /or restored the immunostaining in both protective **(G3&G5)** and therapeutic groups **(G4&G6)**, to nearly normal. Similar observation was observed in nuclei of cells lining the tubules of coda epididymis. Analysis of area density of Ki67 immuno-positive cells provided statistical evidence for such observation (Figs. 5 and 6).

#### 3.3.1. Area percentage of Ki67 immunoexpression in seminiferous and coda epididymal cells

Area percentage of Ki67 immunoexpression in (STs) and coda epididymal cells revealed a significant decrease in the (STs) and coda epididymis in **G2** compared to that in the **G1** rats, whereas there was a significant elevation in **G3** compared to that in the **G2,** while **G4** significant compared to that in the **G3.** Figs. 7 and 8.

#### 3.3.2. Area percentage of Ki67 immunoexpression in coda epididymis

## 4. Discussion

In the present study, plasma glucose levels were considerably lower in both pre-and post-treatment groups who were given ginger water extract. Muhammad & Sangi (2018) reported that aqueous extract of ginger (500 mg/mL) results in an improvement of hyperglycemic status in diabetic rats. Elshater et al. (2009) showed that ginger and its active ingredient; gingerol regulated glucose metabolism by decreasing glycogenolysis and gluconeogenesis with subsequent reductions in hepatic glucose production and blood glucose concentrations.

The present study revealed that cinnamon has a significant hypoglycemic supplement in both protective and therapeutic groups. Similar results were reported previously by Muhammad & Sangi (2018) and recently by Sivapriya & John (2020). Similar results were also obtained by Sahib (2016) and Costello et al. (2016) who found that cinnamon as 1gm/day-controlled blood sugar in diabetic patients.

Costello et al. (2016) suggested that cinnamon work as an anti-diabetic through the activation of insulin receptors via numerous mechanisms including glucose transporter-4 (GLUT-4) and

**Table 1**
The measurement of the (FBG) and (b.w) in different study groups.

| Groups | | Control | diabetic | Ginger | | Cinnamon | |
|---|---|---|---|---|---|---|---|
| | | | | Protective | Therapeutic | Protective | Therapeutic |
| Fasting blood glucose (mg/dl) | 1st week | 81.60 ± 9.92 | 418.20 ± 33.39<br>[a]P = 0.0001 | 155.20 ± 35.51<br>[a]P = 0.001;<br>[b]P = 0.0001 | 418.20 ± 33.39<br>[a]P = 0.0001;<br>[b]P = 1.000 | 155.80 ± 43.72<br>[a]P = 0.0001;<br>[b]P = 0.0001 | 234.80 ± 23.68<br>[a]P = 0.0001;<br>[b]P = 0.0001 |
| | 3rd week | 80.20 ± 6.04 | 478.25 ± 27.38<br>[a]P = 0.0001 | 86.60 ± 9.50<br>[a]P = 0.845;<br>[b]P = 0.0001 | 428.25 ± 122.60<br>[a]P = 0.0001;<br>[b]P = 0.179 | 216.80 ± 22.70<br>[a]P = 0.0001;<br>[b]P = 0.0001 | 252.00 ± 64.58<br>[a]P = 0.0001;<br>[b]P = 0.0001 |
| Body weight (grams) | 1st week | 246.80 ± 8.95 | 301.20 ± 32.00<br>[a]P = 0.001 | 283.40 ± 14.21<br>[a]P = 0.025;<br>[b]P = 0.262 | 301.20 ± 33.00<br>[a]P = 0.001;<br>[b]P = 1.000 | 254.00 ± 9.70<br>[a]P = 0.647;<br>[b]P = 0.005 | 261.80 ± 28.60<br>[a]P = 0.343;<br>[b]P = 0.017 |
| | 3rd week | 312.00 ± 18.16 | 506.65 ± 62.54<br>[a]P = 0.0001 | 428.00 ± 35.15<br>[a]P = 0.002;<br>[b]P = 0.034 | 506.75 ± 62.63<br>[a]P = 0.0001;<br>[b]P = 1.000 | 510.20 ± 38.81<br>[a]P = 0.0001;<br>[b]P = 0.933 | 425.80 ± 57.02<br>[a]P = 0.002;<br>[b]P = 0.030 |

[a] P: significance versus control.
[b] P: significance versus diabetic; data are given as mean +/- standard deviation.

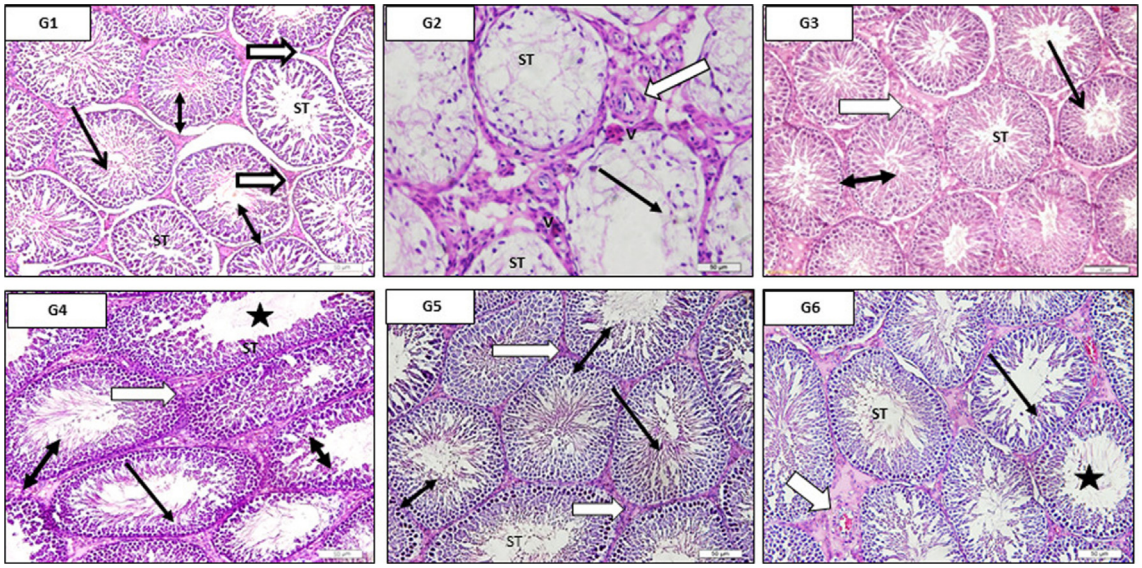



**Fig. 1.** The section in rat testis shows normal seminiferous tubules (ST) of G1; control with its full thickness germ cell layers (double head arrows) and mature sperms, that of G2: diabetic group showing marked degeneration and loss of germ cell layers (black arrows). Interstitial tissue in the G2 group shows hyperplasia of Leydig cells and thickening of blood vessels (white arrow) compared to G1. In most treated groups (G3- G6) preservation of the normal structure of testicular parenchyma (STs & interstitial tissue) observe especially in the G3 (ginger) and G5 (cinnamon) protective groups.

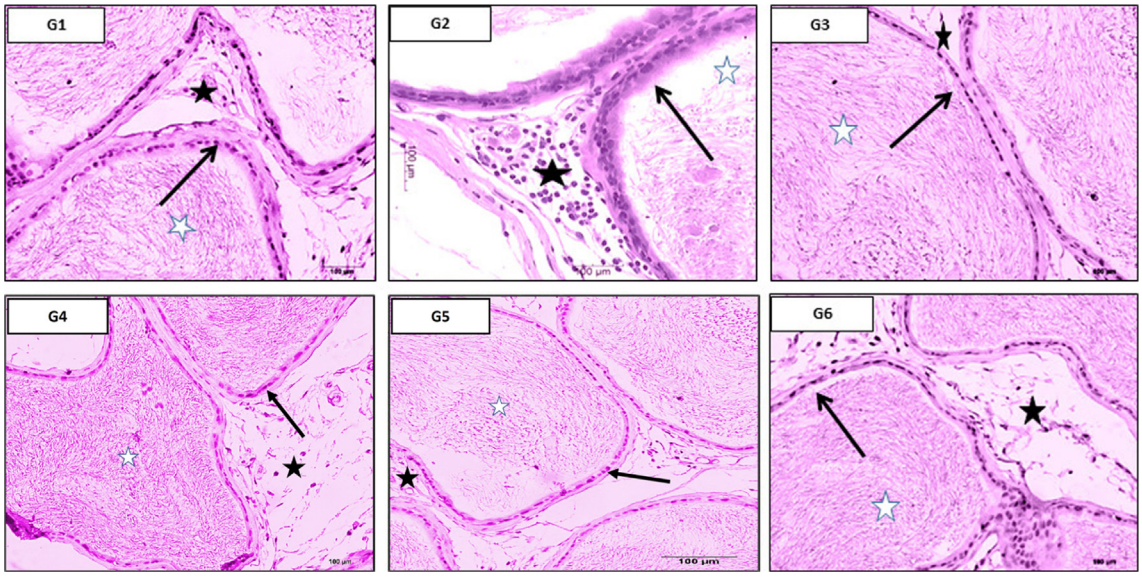


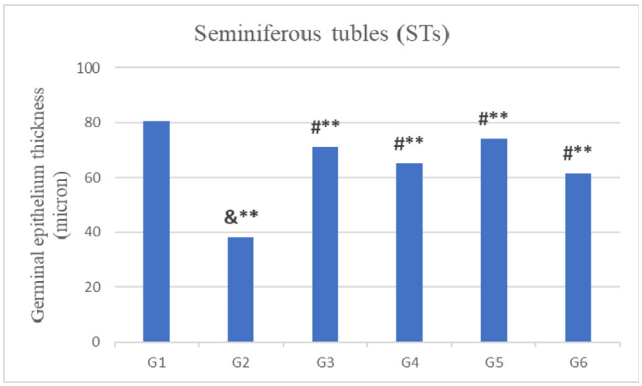

**Fig 2.** (G1-G6) Coda epididymis tissue of a rat from the control group G1 normal tubules with low cuboidal epithelium and a normal population of mature sperms (white star) in the lumen. G2: disorganized epithelium and degenerated nuclei (arrows). decreased sperm population (white star) and inflammatory cells between tubules (black star), G3: normal healthy epithelium (arrows). Full sperm population (white star) and narrow intertubular spaces G4: normal but thinner epithelial lining (arrows). Normal sperm content (white star). wide intertubular spaces, G5 & G6: like control.

increased glycogen synthesis in hepatic tissue. The rise in body weight in diabetic rats in this study might be attributable to mild hyperglycemia (Hardy et al., 2012).

Black et al. (2005) reported the influence of weight changes and gain on impaired glucose tolerance. Ginger either given prior to or after diabetes induction results in insignificant improvement of changes in body weight of diabetic rats. While cinnamon did not significantly alter body weight of diabetic rats.

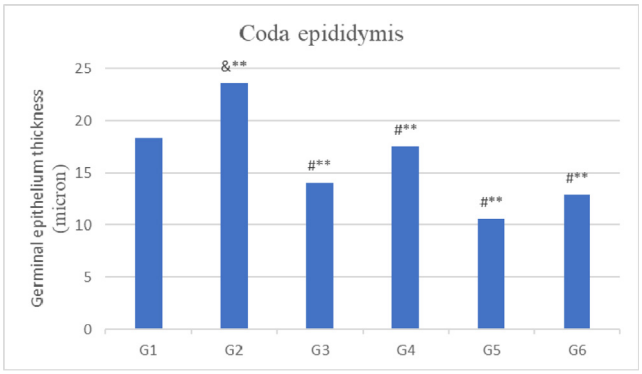
Contradictory data was found in the literature regarding cinnamon's effect on body weight in humans. Other studies reported that Cinnamon has no effect on body weight, but this may be related to the gender and health status of study participants (Mousavi et al., 2020). A histological study in this paper showed that diabetes results in marked degenerative changes in rat testis (seminiferous tubules). Interstitial Leydig cells shows an increased population with thickening of the walls of nearby blood vessels. Similar observations are reported by Al-khamas, (2018) who describes vacuolation of spermatogonia, and a few numbers of primary and secondary spermatocytes while there is degeneration of interstitial Leydig cells in the testes of alloxan-induced diabetes in rats.

Diabetes also is reported by Sánchez-Gutiérrez et al. (2019) to decrease all normal parameters of sperms which confirms the decreased density of sperm observed in both seminiferous tubules and coda epididymis lumina examined in the present study.




&** Sig from G1 P≤0.01, #** Sig from G2 P≤0.01

**Fig. 3.** Morphometric measurement of germinal epithelium thickness of rat (STs) (micron) of **(G1, G2, G3, G4, G5, G6)**.




&** Sig from **G1** P≤0.01, #** Sig from **G2** P≤0.01

**Fig. 4.** Morphometric measurement of the thickness of rat coda epididymis germinal epithelium (micron) of **(G1, G2, G3, G4, G5, G6)**.

Ginger is known to exert an antioxidant activity so uses for the treatment or protection of many diseases including diabetes (Srinivasan, 2017). Ginger is also reported to have many beneficial effects on male fertility; Banihani (2019) finds that ginger increases levels of gonadal testosterone with subsequent improvement of the main sperm parameters. This goes in hand with the preservation and protection of full thickness germ layers in seminiferous tubules of diabetic rats treated or protected by Ginger. The antioxidant activity of Ginger is related to the presence of many substances; gingerols, zingiberene, shogaols as they neutralized oxidative stress enhanced by hyperglycemia in the case of diabetes (Idris et al., 2019).

Cinnamon in this study markedly protected and restored normal seminiferous tubule structure when given prior to or after diabetes induction. Coda epididymis also looked normal with sperm content like control. Khaki, (2015) found that Cinnamon (75 mg/kg/ day) considerably boosted sperm population and quality indicators, according to his findings. The author suggested that this impact is due to cinnamon's antioxidant activity (Shahid et al., 2018). A similar suggestion of its antioxidant protective effect on testis and spermatogenesis was reported by Al-Shawabk & Jamal, (2019). They find a significant improvement of the fertility parameters after cinnamon administration.

In this study, Ki67 immunostaining was used to confirm apoptotic and proliferative changes in spermatogenic cells described in H&E-stained slides. Ki67 expression was decreased in seminiferous tubules of diabetic rats and restored to nearly normal expression in both Ginger and cinnamon treated groups. Cell proliferation in organs with active dividing cells such as testis could be evaluated using the marker Ki-67. Zhao et al. (2018) reported that Ki67 expression is correlated with the status of spermatogenic proliferative rate in seminiferous tubules. Regarding the ginger-induced improvement of Ki67 expression observed in the present study; El-Kott et al. (2014) are found that Ki76 is used to study the role of Zingiber officinale extract-induced improvement of Ki67 expression in kidney tubules as an indicator for regeneration of kidney tubules when used as a preventive and curative supplement in case of acute renal failure induced in rat by Glycerol. Karaca et al. (2015) found that STZ-induced diabetes in rat Ki67 was markedly decreased in seminiferous tubules which is similar to what is find in the present study.

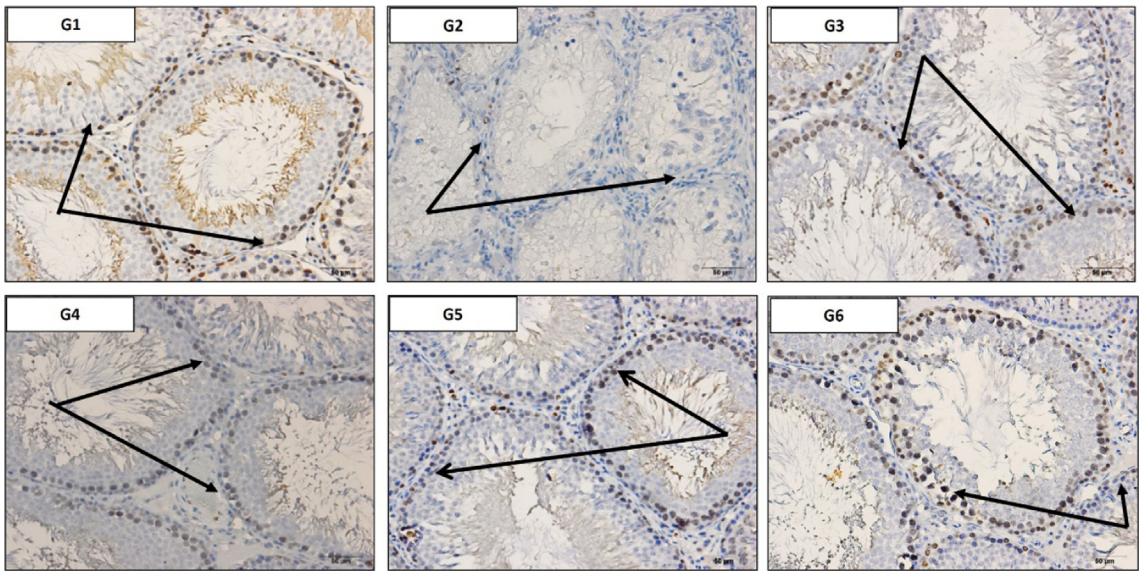



**Fig. 5.** (G1-G6) Seminiferous tubules micrographs immunostained for Ki67(cell proliferating marker) **G1:** High positive immunostaining for Ki67 in spermatogonia of (STs) (arrows), **G2:** absence of Ki67 in (STs), **G3:** high positive immuno-staining for Ki67 in spermatogonia, **G4:** restoration of Ki67 immuno-expression in spermatogonia, **G5 &G6:** positive –immuno-expression in spermatogonia.

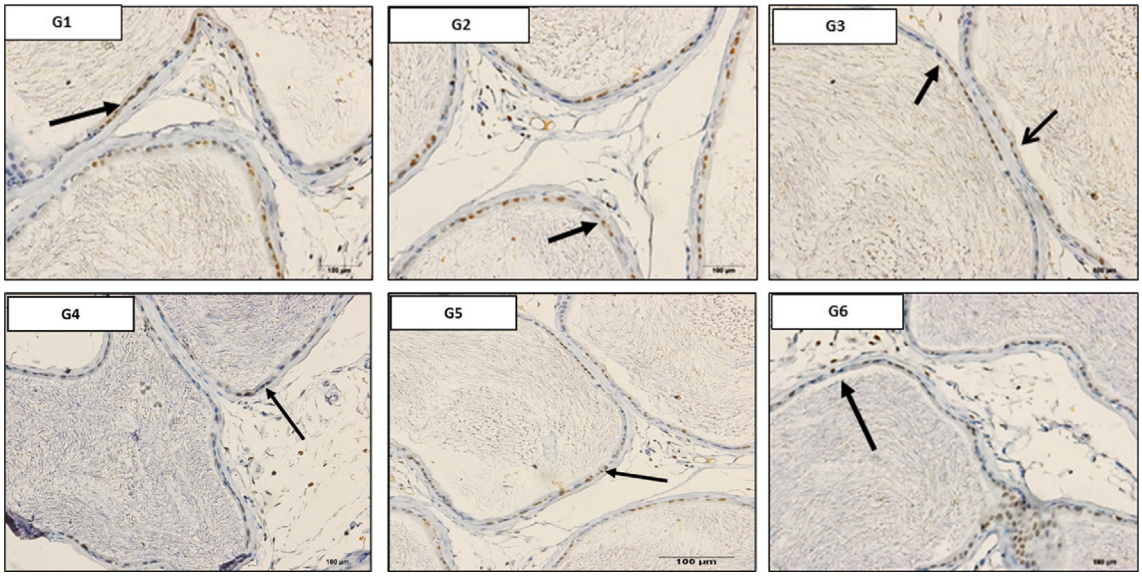
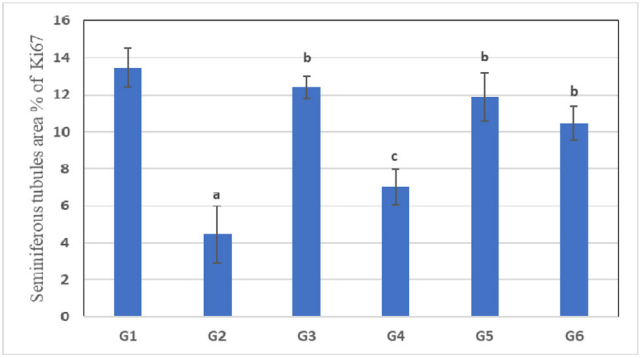
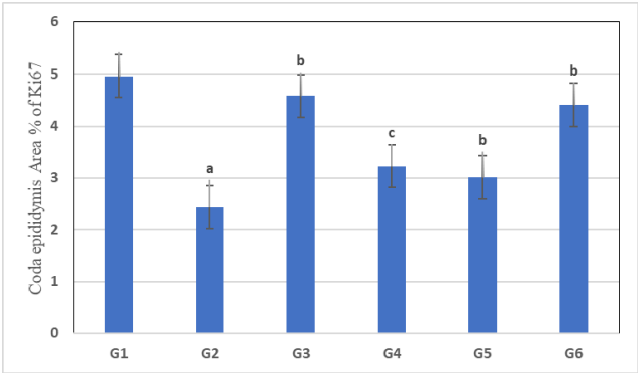



**Fig. 6.** (G1-G6) Coda epididymis micrographs G**1:** High positive Ki67 in lining epithelium, **G2:** absence of Ki67 in lining epithelium, **G3:** high positive Ki67 of lining epithelium, **G4:** restoration of Ki67, **G5 & G6:** positive Ki 67 lining epithelium.




**a** Sig from G1, **b** Sig from G2, **c** Sig from G3

**Fig. 7.** Seminiferous tubules area % of Ki 67 of **(G1, G2, G3, G4, G5, G6)**.




**a** Sig from G1, **b** Sig from G2, **c** Sig from G3

**Fig. 8.** Coda epididymis area % of Ki 67 of **(G1, G2, G3, G4, G5, G6)**.

Karaca et al. (2015) reported that Ki-67 is closely linked to cell growth. As a result, Ki-67 protein expression levels in the testis are the gold standard for spermatogenic cell proliferation and may be used to assess spermatogenic cell proliferation status (Zhao et al., 2018). **In conclusion**, both Ginger and Cinnamon aqueous extracts are effective as both hypoglycemic natural supplements that can protect against diabetic induced testicular damage as well as sharing in the reservation of the cauda epididymal structure and sperm contents. Also, Ki 67 could be considered as a good marker to evaluate apoptotic changes and the regenerative processes in ginger and cinnamon-treated testes which are mostly attributed to their antioxidant effects.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## *Further Reading*

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